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PATENT ABSTRACTS OF JAPAN

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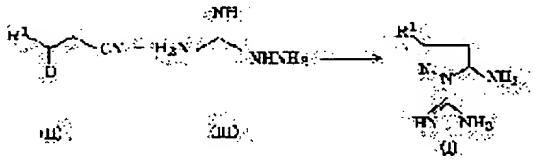
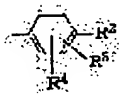
(54) 5-AMINOPYRRAZOLE DERIVATIVE

(57)Abstract:
PURPOSE: To obtain a new 5-aminopyrazole derivative or its salt, having inhibiting activity against the Maillard reaction and useful for preventing and/or treating various diabetic complications and diseases due to aging.
CONSTITUTION: The compound is expressed by formula I {R1 is 3C alkyl, (lower alkyl-substituted)thienyl or furyl, lower alkyl or lower alkenyl substituted with phenyl or phenyl expressed by formula II [R2 to R4 are H, halogen, amino, nitro, (halogenated)alkyl or lower alkoxy], with the proviso that either of R3 and R4 is other than H when R2 is H or Br} or its salt, e.g. 5-amino-3-(1,1-dimethylethyl)-1H-pyrazole-1-carboxamidine hydrochloride. This compound expressed by formula I is obtained by carrying out the cyclizing reaction of an acetonitrile compound expressed by formula III with aminoguanidine salts expressed by formula IV.





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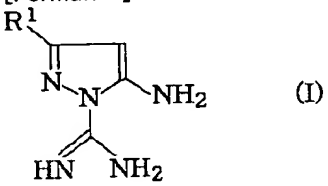
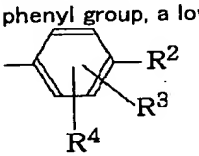
CLAIMS

[Claim(s)]
[Claim 1] A general formula (I)
[Formula 1]



(I)

(The mark in a formula shows following semantics.)
R1 : The low-grade alkyl group which is replaced by the with a carbon numbers of three or more low-grade alkyl group and the low-grade alkyl group, or was replaced by the non-replaced thienyl group or the furil radical, and the phenyl group, a low-grade alkenyl radical, or bottom type [Formula 2]

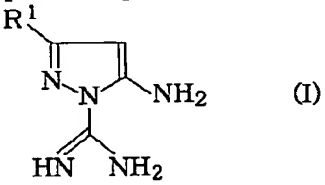


(-- R2, R3, or R4 : -- the same or the phenyl group shown by low-grade alkyl group or lower alkoxy group) which it differs, and is a hydrogen atom, a halogen atom, an amino group, or a nitro group, or may be replaced by the halogen atom, however R2 the case where they are a hydrogen atom or a bromine atom -- R3 And R4 either -- radicals other than a hydrogen atom -- meaning -- 5-amino pyrazol derivative shown or its salt.

[Translation done.]

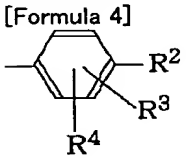
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention has the Maillard inhibition activity and relates to 5-amino pyrazol derivative useful for the prevention and/or the therapy of a disease by various diabetic complications and aging, or its salt.
[0002] In recent years, a close-up of the denaturation of the protein by the glucose is greatly taken as one of the onset factors of diabetic complications, and it is considered to originate in the Maillard reaction produced in the living body. They are a series of reactions considered to result in an advance glycosylation end product (AGE:Advanced GlycationEnd Products) with the decomposition for a Maillard reaction to present [the amino group of protein saccharifies nonenzymatic by the glucose (glycosylation), an AMADORI transition product is formed as an initial glycosylation product, glycosylation advances further and protein constructs a bridge and denaturalizes, and] brown and be refractory, and difficult for it by the protease. or [that advance of the nonenzymatic glycosylation by this reaction or especially generation of AGE protein has a hyperglycemia condition and the slow metabolic rate] — or the protein part which is not metabolized — remarkable — denaturation, depression, and abnormalities of proteins, such as a diabetic's various protein parts, for example, hemoglobin, serum albumin, the collagen and elastin of a connective tissue, myelin, and eyeball RENZUKURISUTARIN It brings and it is thought that it is one of the causes which start the complication of diabetes mellitus, such as a retinopathy, a nephropathy, a cardio-vascular system failure, neuropathy, and a cataract. Moreover, the Maillard reaction in the living body is considered to be one of the mechanisms of aging, and it is guessed that it is what is closely connected also with the disease by aging. Therefore, it is thought very effective in diseases, such as various diabetic complication and a senile disease, to check a Maillard reaction and to control sthenia and AGE generation of nonenzymatic glycosylation, and the development research of the compound which has Maillard reaction inhibition activity conventionally is tried.
[0003] Conventionally, various things are reported as a compound which has Maillard reaction inhibition activity. For example, the aminoguanidine, alpha-hydrazino histidine, the lysines, and such mixture given in JP,62-142114,A reported for the first time as the Maillard reaction inhibitor concerned are mentioned. These drugs suppose that it is what checks secondary glycosylation, as a result can control protein bridge formation and AGE generation by reacting with the carbonyl portion of the AMADORI transition product which is an initial glycosylation product, and blocking this portion.
[0004]
[Problem(s) to be Solved by the Invention] As a result of inventing various Maillard reaction inhibition activity compounds, with the conventional compound, this invention persons find out having the effect excellent in new 5-amino pyrazole which differs in the chemical structure, or its salt, and came to complete this invention.
[0005]
[Means for Solving the Problem] That is, this invention is the following general formula (I).
[0006]
[Formula 3]



(I)

[0007] (The mark in a formula shows following semantics.)
R1 : The low-grade alkyl group which is replaced by the with a carbon numbers of three or more low-grade alkyl group and the low-grade alkyl group, or was replaced by the non-replaced thienyl group or the furil radical, and the phenyl group, a low-grade alkenyl radical, or bottom type [0008]
[Formula 4]



[0009] They are 5-amino pyrazol derivative shown in (either R3 and R4 mean radicals other than a hydrogen atom when it differs, and it is a hydrogen atom, a halogen atom, an amino group, or a nitro group or R2, R3, R4:identitas, the low-grade alkyl group that may be replaced by the halogen atom or a lower alkoxy group, however R2 are a hydrogen atom or a bromine atom), or its salt.

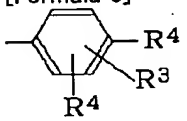
[0010] Hereafter, it explains to details per this invention compound. In the definition of the general formula of this specification, especially the term that "low-grade" Becomes unless it refuses means the straight chain whose carbon numbers are 1 thru/or six pieces, or the chain of the letter of branching. As a "low-grade alkyl group", a methyl group, an ethyl group, a propyl group, an isopropyl group, butyl, an isobutyl radical, sec-butyl, tert-butyl, a pentyl radical, an isopentyl radical, a neopentyl radical, a tert-pentyl radical, 1-methylbutyl radical, 2-methylbutyl radical, 1, 2-dimethyl propyl group, a hexyl group, an iso hexyl group, etc. are specifically mentioned.

[0011] As a "low-grade alkenyl radical", a carbon number is the alkenyl radical which are 2 thru/or six pieces, and a vinyl group, an allyl group, 1-propenyl radical, a butenyl group, a pentenyl radical, a hexenyl radical, etc. are specifically mentioned. As a "lower alkoxy group", a methoxy group, an ethoxy radical, a propoxy group, an isopropoxy group, a butoxy radical, an iso butoxy radical, a sec-butoxy radical, a tert-butoxy radical, a pentyloxy (amyloxy) radical, an isopentyloxy radical, a tert-pentyloxy radical, a neopentyl oxy-radical, 2-methyl propoxy group, 1, 2-dimethyl propoxy group, 1-ethyl propoxy group, a hexyloxy radical, etc. are mentioned.

[0012] As "a with a carbon numbers of three or more low-grade alkyl group" in R1, it is desirable, and the alkyl groups whose carbon numbers are 3 thru/or six pieces are a propyl group, butyl, a pentyl radical, a hexyl group, etc., and, specifically, are a propyl group, butyl, and a pentyl radical suitably. As "the thienyl group replaced by the low-grade alkyl group, or a furil radical", it is the thienyl group or furil radical replaced by the one above-mentioned low-grade alkyl group, and they are specifically 2-methyl thienyl group, 2-ethyl thienyl group, 2-propyl thienyl group, 2-methyl furil radical, 2-ethyl furil radical, 2-propyl furil radical, etc. As "the low-grade alkyl group replaced by the phenyl group, or a low-grade alkenyl radical", it is the above-mentioned low-grade alkyl group or low-grade alkenyl radical replaced by one phenyl group, and they are specifically benzyl, a phenethyl radical, 3-phenylpropyl radical, 2-phenyl ethenyl radical, 3-phenyl allyl group, a 3-phenyl-1-propenyl radical, etc.

Bottom type [0013]

[Formula 5]



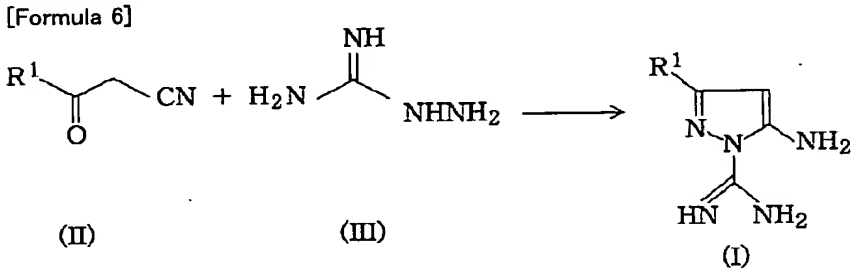
[0014] The inside R2 of the phenyl group come out of and shown, and R3 Or R4 As a "halogen atom" which can be set, a fluorine atom, a chlorine atom, a bromine atom, etc. are mentioned. As "the low-grade alkyl group replaced by the halogen atom, or a lower alkoxy group", it is the above-mentioned low-grade alkyl group or above-mentioned lower alkoxy group replaced by the above-mentioned halogen atom, and they are specifically a monochloro methyl group, a mono-fluoro methyl group, a trifluoromethyl radical, a trifluoro ethyl group, a monochloro methoxy group, a mono-fluoro methoxy group, a trifluoro methoxy group, etc.

[0015] this invention compound (I) can form an acid and a salt. As this acid, an acid addition salt with organic acids, such as an acid addition salt with mineral acids, such as a hydrochloric acid, a hydrobromic acid, a hydroiodic acid, a sulfuric acid, a nitric acid, and a phosphoric acid, a formic acid, an acetic acid, a propionic acid, butanoic acid, oxalic acid, a malonic acid, a succinic acid, a maleic acid, a fumaric acid, a lactic acid, a malic acid, a tartaric acid, carbonic acid, glutamic acid, and an aspartic acid, is mentioned. Moreover, isolation of this invention compound (I) may be carried out as material of a hydrate, solvates, such as ethanol, or a crystal polymorphism, and these invention is also included in this invention.

(Manufacturing method) this invention compound can be manufactured with the application of various synthesis methods. The typical manufacturing method is illustrated below.

The 1st process [0016]

[Formula 6]



(II) (III) (I)

[0017] (R1 shows above semantics among a formula.) By the acetonitrile compound shown by the general formula (II), and aminoguanidine salts (III), this invention compound (I) performs ring closure, and is manufactured. This ring closure is performed under heating thru/or heating reflux among a solvent in an acetonitrile compound (II) and the aminoguanidine salts (III) of the reaction equivalent amount. As said solvent, a methanol, ethanol, THF and DMF, or an acetic acid is mentioned. A hydrochloride, a bromate salt, or a nitrate is mentioned as an acid addition salt of

aminoguanidine.
[0018] The 2nd process (reduction)
Inside R1 of this invention compound The compound which is the low-grade alkyl group replaced by the phenyl group or R2, R3, and R4 The compound whose either is an amino group is R1. The compound which is the low-grade alkenyl radical replaced by the phenyl group or R2, R3, and R4 Either performs the reduction reaction of the compound which is a nitro group, and is manufactured. In the case of the low-grade alkyl group replaced by the phenyl group, by catalytic hydrogenation, it is carried out to the bottom of ordinary pressure thru/or pressurization in solvents usually used, such as a methanol, ethanol, and ethyl acetate, under existence of the precious metal catalyst of palladium carbon, platinum oxide, etc. that this reduction reaction should just follow a conventional method. moreover, the case of the amino group -- metals, such as iron, zinc, and tin, — using -- warming under ordinary temperature in a solvent, such as hydrochloric-acid, acetic-acid, ammonium chloride's, etc. existence sewage or an acetic acid, — it is carried out downward.
[0019]
[Effect of the Invention] this invention compound (I) or its salt has Maillard reaction inhibition activity, and is useful for the prevention and/or the therapy of arteriosclerosis, the arthrosclerosis, etc. which are considered that cardio-vascular system failures, such as various diabetic complications, for example, a retinopathy, a nephropathy, a coronary artery nature heart disease, peripheral circulatory disturbance, and cerebrovascular disease, the diabetes-mellitus sexual nerosis, a cataract, and a Maillard reaction are involving. Moreover, prevention of the atherosclerosis and the senile cataract which are considered to cause by aging of protein, or cancer, and/or the usefulness as a remedy are also expected. Furthermore, since it is possible to prevent protein bridge formation of a collagen, an elastin, etc., it can also consider as cosmetics or skin external preparations. It is common knowledge that the Maillard reaction relates to deterioration of the protein of not only in the living body but ingesta or a taste object and amino acid, and the drugs of this invention can be used only as functional food for said physic and the cosmetics purpose further again also as Maillard reaction inhibitor of the ingesta containing protein or amino acid, or a taste object.
[0019] (The pharmacology effect) The Maillard reaction inhibition activity of this invention is checked by the following experiment methods, and has the outstanding effect.
After having dissolved the Maillard reaction inhibition activity test experiment method lysozyme and the ribose in the 0.1M sodium phosphate buffer solution (pH7.4) containing sodium-azide 3mM so that it might become the concentration of 6mg [ml] /and 100mM(s), respectively, and carrying out incubation for seven days at 37 degrees C, electrophoresis was performed for the constant rate using ejection SDS-PAGE. The quantum of the amount of generation of a dimer and a trimer was carried out with the densitometer after dyeing by Coomassie Brilliant Blue R -250 0.04% after electrophoresis. It added so that it might be set to 1mM, 3mM, 10mM, or 30mM(s) before an incubation, and the compound of this invention investigated the depressor effect over the dimer and trimer generation in each concentration, and calculated IC50 value.
[0020] (Pharmaceutical preparation-ized matter) The physic constituent which contains one sort, such as a compound shown by the general formula (I), or the salt permitted pharmaceutically, a hydrate permitted pharmaceutically, or two sorts or more as an active principle Usually, using the support and the excipient for pharmaceutical preparation which are used, and other additives, it is prepared by a tablet, powder, a fine grain agent, a granule, a capsule, a pill, liquids and solutions, injections, suppositories, ointment, patches, etc., and a medicine is prescribed for the patient taking-orally-wise or parenterally. although the clinical dose to the Homo sapiens of this invention compound is suitably determined in consideration of a patient's symptom, weight, age, sex, etc. which are applied — usually -- an adult — per day, in taking orally, it is 10-200mg preferably, and 0.1-500mg is 1 time about this — it is — a medicine is prescribed for the patient in several steps. Since a dose is changed on condition that versatility, an amount smaller than the above-mentioned dose range may be enough as it.
[0021] A tablet, powder, a granule, etc. are used as a solid-state constituent for internal use by this invention. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, a lactose, a mannitol, grape sugar, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate. The constituent may contain a solubilizing agent like additives other than an inactive diluent, for example, lubricant like magnesium stearate and disintegrator like a calcium carboxymethyl cellulose, a stabilizing agent like a lactose, glutamic acid, or an aspartic acid according to a conventional method. The coat of a tablet or the pill may be carried out as occasion demands with the film of stomach solubility, such as cane sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or enteric material.
[0022] The liquid constituent for internal use contains the inactive diluent generally used, for example, purified water, and ethanol including the opacifier permitted in drugs, a solution agent, suspension, syrups, elixirs, etc. This constituent may contain solubilization thru/or a solubilizing agent, a wetting agent, an adjuvant like suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent. As injections for parenteral administration, the sterile solution agent of aquosity or nonaqueous nature, suspension, and an opacifier are included. As a water solution agent and suspension, distilled water for injections and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80 (trade name), etc., for example. Such a constituent may also contain an additive still like an isotonizing agent, antiseptics, a wetting agent, an

emulsifier, a dispersant, a stabilizing agent (for example, lactose), solubilization, or a solubilizing agent. These are sanitized by the combination or the exposure of filtration and a germicide which lets for example, a bacteria hold filter pass. These manufacture a sterile solid-state constituent again, and they can also use it for sterile water or the sterile solvent for injection before use, dissolving. In addition, when preparing the Maillard reaction inhibition compound of this invention as cosmetics or skin external preparations, it blends so that 0.05-10 weight section content of this invention compound (I) and its salt may be carried out to the whole pharmaceutical preparation. Cosmetics and skin external preparations can be prepared with a conventional method using a general cosmetics basis or an external use basis. Moreover, the Maillard reaction inhibition compound of this invention can also be prepared as ingesta, a taste object, functional food, etc. with a conventional method.

[0023]

[Example] Hereafter, although an example explains this invention to details further, this invention is not limited to these examples.

The heating reflux of the solution of example 1 pivaloyl acetonitrile 1.26g, methanol of 1.37g of aminoguanidine hydrochlorides 15ml, and 15ml of acetic acids was carried out for 5 hours. After it distilled off the solvent under reduced pressure and the silica gel chromatography (chloroform: eluate; methanol = 5:1) refined the obtained residue, it recrystallized from the ethanol-ether and 0.74g of 5-amino-3-(1 and 1-dimethyl ethyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides was obtained.

[0024] physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

5.59 (1H, s) delta:1.22 (9H, s), 8.79 (4H, br)

The following examples 2 thru/or the compound of 18 were obtained like the example 1.

[0025] example 25-amino-3-(2-phenyl ethenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: -- a cinnamoyl acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:5.99 (1H, s) and 6.87- 7.68 (7H, m) and 9.01 (4H, br)

[0026] example 35-amino-3-(2-thienyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: -- 2-CHIENOIRU acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:5.98 (1H, s), 7.09-7.19 (1H, m), and 7.54- 7.66 (2H, m) and 8.95 (4H, br)

[0027] example 45-amino-3-(2-furil)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: -- a 2-furoyl acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

7.81 (1H, d, J= 1Hz) delta:5.92 (1H, s), 6.60-6.65 (1H, m), 6.94-6.98 (1H, m), 9.21 (4H, br)

[0028] example 55-amino-3-(2-methyl-3-furil)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (2-methyl-3-furoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:2.52 (3H, s), 5.85 (1H, s), 6.75 (1H, d, J= 2Hz), 7.57 (1H, d, J= 2Hz), 9.02 (4H, br)

[0029] example 65-amino-3-(4-methylphenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-methyl benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:2.35 (3H, s), 6.07 (1H, s), 7.27 (2H, d, J= 8Hz), 7.77 (2H, d, J= 8Hz), 8.88 (4H, br)

[0030] example 75-amino-3-(3-trifluoro methylphenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (3-trifluoromethyl benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:6.23 (1H, s), 7.61-7.77 (2H, m), and 8.13- 8.26 (2H, m) and 9.17 (4H, br)

[0031] example 85-amino-3-(4-trifluoro methylphenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-trifluoromethyl benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:6.18 (2H, s), 6.44 (2H, br), 7.83 (2H, d, J= 8.5Hz), 8.10 (2H, d, J= 8.5Hz), 9.29 (4H, brs)

[0032] example 95-amino-3-(4-methoxypheny)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-methoxy benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:3.80 (3H, s), 6.04 (1H, s), 7.01 (2H, d, J= 9Hz), 7.81 (2H, d, J= 9Hz), 9.02 (4H, br)

[0033] example 105-amino-3-(4-trifluoro methoxypheny)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-trifluoro methoxy benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

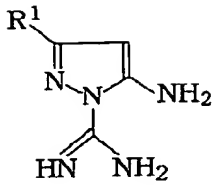
delta:6.13 (1H, s), 6.43 (2H, brs), 7.46 (2H, d, J= 8Hz), 8.01 (2H, d, J= 8Hz), 9.27 (4H, br)

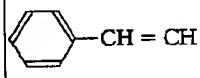
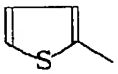
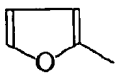
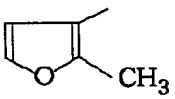
[0034] example 115-amino-3-(4-fluoro phenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-fluoro benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)

delta:6.09 (1H, s), 7.20-7.40 (2H, m), and 7.85- 8.02 (2H, m) and 9.05 (4H, br)

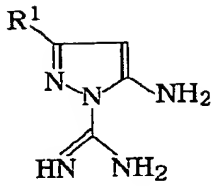
[0035] example 125-amino-3-(3-chlorophenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (3-chloro benzoyl) -- an acetonitrile -- physicochemical -- description -- a

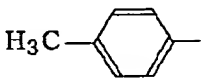
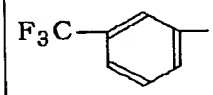
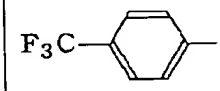
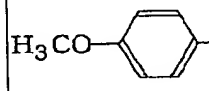
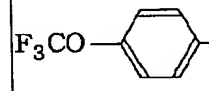
nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta: -- 6.16 (1H, s), 6.42 (2H, br), 7.49-7.52 (2H, m), 7.82-7.84 (1H, m), and 7.99 (1H, s) and 9.25 (4H, br)
[0036] example 135-amino-3-(4-chlorophenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-chloro benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:6.11 (1H, s), 7.53 (2H, d, J= 8.5Hz), 7.91 (2H, d, J= 8.5Hz), 9.21 (4H, br)
[0037] example 145-amino-3-(4-nitrophenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (4-nitrobenzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:6.22 (1H, s), 8.15 (2H, d, J= 8.5Hz), 8.32 (2H, d, J= 8.5Hz), 9.31 (4H, br)
[0038] example 155-amino-3-(3, 4-dimethoxy phenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (3, 4-dimethoxybenzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:3.80 (3H, s), 3.83 (3H, s), 6.08 (1H, s), 7.02 (1H, d, J= 8Hz), 7.39 (1H, d, J= 8Hz), 7.48 (1H, s), 9.07 (4H, br)
[0039] example 165-amino-3-(3, 4, 5-trimethoxyphenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (3, 4, 5-trimethoxybenzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:3.68 (3H, s), 3.83 (6H, s), 6.31 (1H, s), 7.22 (2H, s), 7.98 (4H, br)
[0040] example 175-amino-3-(3-methylphenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: (3-methyl benzoyl) -- an acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6) The TMS internal standard delta:2.37 (3H, s), 6.08 (1H, s) and 7.24 (1H, d, J= 7.3Hz), 7.33-7.36 (1H, m), 7.66 (1H, d, J= 7.8Hz), 7.71 (1H, s), 9.18 (4H, br)
[0041] example 185-amino-3-propyl-1H-pyrazole-1-cull BOKISAMIJIN hydrochloride raw material compound: -- a butanoyl acetonitrile -- physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:0.91 (3H, t, J= 7.3Hz), 1.54-1.63 (2H, m), 2.43 (2H, t, J= 7.5Hz), 5.54 (1H, s), 6.15 (2H, brs), 8.98 (4H, brs)
[0042] 0.1g of 10% palladium-carbon was added to the methanol 40ml solution of 0.6g of example 195-amino-3-(2-phenyl ethenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides, and it agitated for 30 minutes under the ordinary pressure hydrogen ambient atmosphere and the room temperature. After filtering reaction mixture and removing insoluble matter, reduced pressure distilling off of the solvent was carried out. The obtained residue was recrystallized from the ethanol-ether and 0.38g of 5-amino-3-(2-phenylethyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides was obtained.
physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:2.64- 3.04 (4H, m), 5.55 (1H, s), and 7.09- 7.39 (5H, m) and 8.88 (4H, br), [0043] The 10% palladium-carbon of the amount of catalysts was added to the methanol 40ml solution of 0.24g of example 205-amino-3-(4-nitrophenyl)-1H-pyrazole-1-cull BOKISAMIJIN hydrochlorides, and it agitated for 30 minutes under the ordinary pressure hydrogen ambient atmosphere and the room temperature. After filtering reaction mixture and removing insoluble matter, 0.5ml of 4-N hydrochloric-acid-dioxane solutions was added. Reduced pressure distilling off of the solvent was carried out, the obtained residue was recrystallized from the ethanol-ether, and 0.16g of 5-amino-3-(4-aminophenyl)-1H-pyrazole-1-cull BOKISAMIJIN 2 hydrochlorides was obtained.
physicochemical -- description -- a nuclear-magnetic-resonance spectrum (DMSO-d6, TMS internal standard)
delta:6.06 (1H, s), 7.22 (2H, J= 8.5Hz), 7.85 (2H, d, J= 8.5Hz), 9.14 (4H, br)
[0044]
[A table 1]



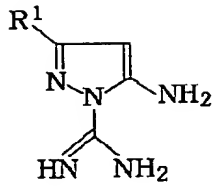
実施例番号	R^1	塩	理化学的性状
1	$(CH_3)_3C-$	HCl	mp.197～201℃ Anal.($C_8H_{16}N_5Cl \cdot 0.1H_2O$として) C: 理論値(%) 43.78, 実験値(%) 43.71 H: 理論値(%) 7.44, 実験値(%) 7.36 N: 理論値(%) 31.91, 実験値(%) 32.08 Cl: 理論値(%) 16.15, 実験値(%) 16.31 Mass (m／z)： 181 $(M-HCl)^+$
2		HCl	mp.209～210℃ Anal.($C_{12}H_{14}N_5Cl$として) C: 理論値(%) 54.65, 実験値(%) 54.56 H: 理論値(%) 5.35, 実験値(%) 5.32 N: 理論値(%) 26.56, 実験値(%) 26.50 Cl: 理論値(%) 13.44, 実験値(%) 13.24 Mass (m／z)： 227 $(M-HCl)^+$
3		HCl	mp.179～182℃ Anal.($C_8H_{10}N_5OClS \cdot 0.4H_2O$として) C: 理論値(%) 38.29, 実験値(%) 38.60 H: 理論値(%) 4.34, 実験値(%) 4.12 N: 理論値(%) 27.91, 実験値(%) 27.65 Cl: 理論値(%) 14.13, 実験値(%) 14.24 Mass (m／z)： 207 $(M-HCl)^+$
4		HCl	mp.187～190℃ Anal.($C_8H_{10}N_5Cl$として) C: 理論値(%) 42.21, 実験値(%) 41.81 H: 理論値(%) 4.43, 実験値(%) 4.39 N: 理論値(%) 30.76, 実験値(%) 30.75 Cl: 理論値(%) 15.57, 実験値(%) 15.38 Mass (m／z)： 191 $(M-HCl)^+$
5		HCl	mp.178～181℃ Anal.($C_9H_{12}N_5OCl \cdot 0.1H_2O$として) C: 理論値(%) 44.40, 実験値(%) 44.44 H: 理論値(%) 5.05, 実験値(%) 5.01 N: 理論値(%) 28.76, 実験値(%) 28.51 Cl: 理論値(%) 14.56, 実験値(%) 14.26 Mass (m／z)： 205 $(M-HCl)^+$

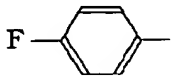
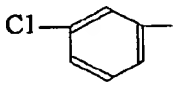
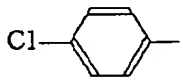
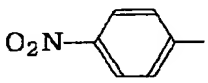
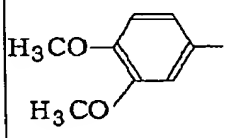
[0045]
[A table 2]



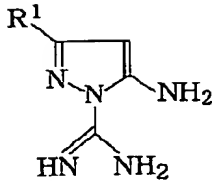
実施例番号	R^1	塩	理化学的性状
6		HCl	mp.178～181℃ Anal.($C_{11}H_{14}N_5Cl \cdot 0.2H_2O$として) C H N Cl 理論値(%) 51.75 5.68 27.43 13.89 実験値(%) 51.92 5.67 27.03 13.97 Mass (m/z): 215 $(M-HCl)^+$
7		HCl	mp.209～212℃ Anal.($C_{11}H_{11}N_5F_3Cl$として) C H N Cl F 理論値(%) 43.22 3.63 22.91 11.60 18.64 実験値(%) 43.02 3.61 22.98 11.70 18.42 Mass (m/z): 269 $(M-HCl)^+$
8		HCl	mp.189～192℃ Anal.($C_{11}H_{11}N_5F_3Cl$として) C H N Cl F 理論値(%) 43.22 3.63 22.91 11.60 18.64 実験値(%) 42.91 3.62 23.01 11.53 18.47 Mass (m/z): 269 $(M-HCl)^+$
9		HCl	mp.184～187℃ Anal.($C_{11}H_{14}N_5OCl$として) C H N Cl 理論値(%) 49.35 5.27 26.16 13.24 実験値(%) 49.16 5.35 25.97 13.23 Mass (m/z): 231 $(M-HCl)^+$
10		HCl	mp.182～185℃ Anal.($C_{11}H_{11}N_5ClF_3O \cdot 0.4H_2O$として) C H N Cl 理論値(%) 40.17 3.62 21.29 10.78 実験値(%) 40.36 3.61 21.00 10.62 Mass (m/z): 285 $(M-HCl)^+$

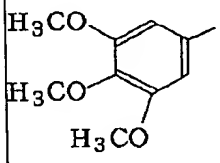
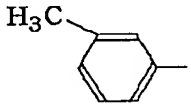
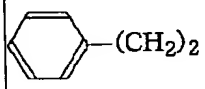
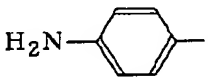
[0046]
[A table 3]



実施例番号	R^1	塩	理化学的性状
11		HCl	mp.194～198℃ Anal.($C_{10}H_{11}N_5ClF \cdot 0.2H_2O$として) C H N Cl F 理論値(%) 46.32 4.43 27.01 13.67 7.33 実験値(%) 46.11 4.31 27.09 13.55 7.25 Mass (m/z): 219 $(M-HCl)^+$
12		HCl	mp.192～194℃ Anal.($C_{10}H_{11}N_5Cl_2 \cdot 0.2C_2H_6O$として) C H N 理論値(%) 44.40 4.37 24.89 実験値(%) 44.07 4.36 24.55 Mass (m/z): 235 $(M-HCl)^+$
13		HCl	mp.192～195℃ Mass (m/z): 235 $(M-HCl)^+$
14		HCl	mp.205～207℃ Anal.($C_{10}H_{11}N_6O_2Cl$として) C H N Cl 理論値(%) 42.49 3.92 29.73 12.54 実験値(%) 42.26 3.81 29.84 12.50 Mass (m/z): 246 $(M-HCl)^+$
15		HCl	mp.208～210℃ Anal.($C_{12}H_{16}N_5O_2Cl$として) C H N Cl 理論値(%) 48.41 5.42 23.52 11.91 実験値(%) 48.34 5.46 23.45 11.86 Mass (m/z): 261 $(M-HCl)^+$

[0047]
[A table 4]



実施例番号	R^1	塩	理化学的性状
16		HCl	mp.199～202℃ Mass (m/z) : 291 $(M-HCl)^+$
17		HCl	mp.192～194℃ Anal.($C_{11}H_{14}N_5Cl \cdot 0.3C_2H_6O$として) C H N Cl 理論値(%) 52.47 6.00 26.37 13.35 実験値(%) 51.99 5.95 26.29 13.07 Mass (m/z) : 215 $(M-HCl)^+$
18	$CH_3CH_2CH_2-$	HCl	mp.166～167℃ Mass (m/z) : 167 $(M-HCl)^+$
19		HCl	mp.187～189℃ Anal.($C_{12}H_{16}N_5Cl \cdot 0.2H_2O$として) C H N Cl 理論値(%) 53.51 6.14 26.00 13.16 実験値(%) 53.36 6.07 25.95 13.43 Mass (m/z) : 229 $(M-HCl)^+$
20		2HCl	mp.219～222℃ Anal.($C_{10}H_{14}N_6Cl_2 \cdot 0.2H_2O$として) C H N Cl 理論値(%) 41.03 4.96 28.71 24.22 実験値(%) 41.10 4.91 28.64 24.42 Mass (m/z) : 217 $(MH-2HCl)^+$

[Translation done.]